Bulletin of the World Health Organization, 58 (1): 37-41 (1980)

Does BCG vaccination protect the newborn and young infants?*

H. G. TEN DAM[1] & K. L. HITZE[2]

In recent years, BCG vaccination has been applied to the newborn in many immunization programmes at the time of the changeover from mass vaccination to an integrated programme. Whereas the efficacy of BCG vaccination in adolescents and adults has been studied in a number of controlled trials, there is very little direct evidence of the efficacy of BCG vaccination against infant tuberculosis. This article reviews the evidence that is available concerning vaccination of the newborn from both controlled trials and retrospective studies. Further controlled prospective studies and epidemiological surveillance of BCG vaccination in infancy are highly indicated.

During the last few decades, BCG vaccination has been applied on an ever-increasing scale. Campaigns have usually been initiated with an extensive mass campaign to cover the eligible population in a short time, and this has been followed by a programme integrated with the general health services to keep up with the birth rate and thus maintain and possibly increase the coverage obtained. In many of the maintenance programmes, vaccination is therefore directed to the youngest age groups—including the newborn.

Among the advantages of this strategy are that all children are vaccinated before being exposed to infection and that protection is afforded against the serious forms of childhood tuberculosis—miliary tuberculosis and tuberculous meningitis—which are still often fatal, even when chemotherapy is available. On the other hand it is generally considered that a single vaccination at birth does not give protection for life, and that revaccination is necessary at school age.

Although vaccination with BCG is now being applied to the newborn, there is very little direct evidence concerning the degree of protection afforded to very young infants. Most of the evidence of the efficacy of BCG vaccination comes from clinical observations in adolescents and young adults, and much of it has been contradictory. Several studies have been reviewed recently, and the reasons for the differences in protection remain unknown.[a,b]

Experience has, in fact, shown that the response to BCG vaccination in the newborn is not necessarily the same as in adolescents and young adults, since the immediate response to BCG and the clinical types of tuberculosis in the two age groups are different. A dose of BCG that is well tolerated in schoolchildren often causes suppurative lymphadenitis in a high proportion of the newborn. Whereas this, unlike the local reaction at the site of vaccination, could be taken to indicate a good "take" of the vaccination, the resulting post-vaccination tuberculin sensitivity in the newborn invariably appears to be lower than in older children given the same dose of BCG. This indicates that the immunological response is relatively low, and thus that protection may be less. Moreover, in order to avoid an

* A French version of this article will appear in a later issue of the *Bulletin*.

[1] Scientist, Tuberculosis and Respiratory Infections, Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

[2] Chief Medical Officer, Tuberculosis and Respiratory Infections, WHO, Geneva.

[a] TEN DAM, H. G. ET AL. *Bulletin of the World Health Organization*, 54: 255 (1976).

[b] TUBERCULOSIS PREVENTION TRIAL, *Bulletin of the World Health Organization*, 57: 819 (1979).

unacceptably high incidence of suppurative lymphadenitis in programmes directed specifically to the lowest age group, the dose of BCG vaccine is usually reduced, and this results in a further decrease of the immunological response as evidenced by the post-vaccination tuberculin sensitivity.

This article reviews the evidence from three controlled trials that have involved the vaccination of the newborn, all carried out in the 1930s, and also the only recent evidence that is available on this question which comes from retrospective studies.

CONTROLLED TRIALS IN THE NEWBORN

The first attempt to examine the efficacy of BCG vaccination of young infants in a controlled trial was started in 1926 in New York City.[c] Up to 1933, half of the infants (under 1 year old, many under 4 weeks) referred from tuberculous homes were vaccinated, the others serving as controls. During this period the results were extremely favourable: there were 3 deaths from tuberculosis among 445 vaccinated children but 18 deaths among 545 controls. However, the allocation to the vaccinated group and the control group was not at random but by selection, and it was realized that this could have biased the result. From 1933 onwards, therefore, infants were allocated to the vaccination and control groups alternately. From then on, the efficacy of BCG vaccination appeared to diminish: up to 1944, 8 children died from tuberculosis among the 566 who were vaccinated, and 8 died among the 528 controls. However, in the control group 49 were lost to follow-up, whereas in the vaccinated group only 29 children were lost; this significant difference could have biased the result. Also, in this trial, the BCG strain became contaminated in 1932 and it is possible that the strain was modified during the back-selection process. Another point worth mentioning is that, contrary to Calmette's recommendations and to the practice in later trials, the infants were not systematically isolated before and after vaccination. Some children, therefore, may have been infected before immunity could develop. Among the children who were fortuitously isolated, there were 3 deaths among 96 controls and only 1 death among 91 vaccinated children.

In 1933, Ferguson & Simes started a controlled trial in Saskatchewan Indians.[d] Infants were vaccinated intradermally (21 orally) within 10 days of birth. The intake lasted until the end of 1945. Allocation to the vaccinated and the control groups was by paired families, with annual rotation. According to the authors, this procedure resulted in balanced groups of 306 vaccinated children and 303 controls: the general mortality in the first year of life was 12.7% among those vaccinated and 12.5% among the controls. During the 14 years of the study there were 53 deaths among those vaccinated with BCG and 63 among the controls. Among the 306 vaccinated children, there were 6 cases of tuberculosis, 2 of whom died. Among the 303 controls, there were 29 cases, 9 of whom died. Thus the degree of protection observed was over 80%.

A study of BCG vaccination of the newborn by a percutaneous multiple puncture method was started by Rosenthal et al. in 1937.[e] It comprised 3381 infants of whom about half were vaccinated during the first week after birth if the household members were free from tuberculosis. (Vaccinated infants were also included in some instances when a household member was at first suspected of having tuberculosis but within 3 months showed a cleared X-ray picture.) The statistical analysis presented by the authors showed that the two groups were not entirely comparable, since there was an excess of follow-up among the vaccinated subjects under 2 years of age and among the control subjects over 2 years of age. The

[c] LEVINE, M. I. *Pediatrics*, **15**: 288 (1949).

[d] FERGUSON, R. G. & SIMES, A. B. *Tubercle*, **30**: 5 (1949).

[e] ROSENTHAL, S. R. ET AL. *Pediatrics*, **28**: 622 (1961).

investigators considered that these differences should not have influenced the observed morbidity and mortality data, a viewpoint they substantiated by showing that the morbidity from measles, whooping cough, and other childhood diseases was the same in both groups. As regards tuberculosis, however, the difference in morbidity was highly significant: there were 17 cases (including 1 death) among the 1716 vaccinated and 65 cases (including 6 deaths) among the 1665 controls—75% protection.

RETROSPECTIVE STUDIES

Retrospective studies are well known to be subject to observer bias, an important aspect of which is that investigators often set out to prove a certain concept and accordingly select their material. The use of modern electronic data processing equipment greatly facilitates such a biased selection, since large amounts of data can be made available easily and many "hypotheses" can be tested or even formulated after inspection of the material. Another form of bias stems from a preference to report success rather than failure. Retrospective studies, therefore, are best considered to attain validity only if they are confirmed repeatedly.

Mortality and morbidity statistics are frequently used to show the impact of a certain health measure. However, such data should be interpreted with caution since a statistical association between the application of a health measure and morbidity or mortality does not necessarily indicate cause and effect; both events may, for example, be associated with another factor. This no doubt applies in tuberculosis epidemiology. In European countries, for which fairly reliable statistics are available, there has been a steady decline in tuberculosis morbidity and mortality since the beginning of the century. This decline is often referred to as "natural" or is explained as a result of better living conditions; it could also result, at least partly, from the practice of isolating tuberculosis patients in sanatoria and thus eliminating the sources of infection. Be this as it may, it would clearly be incorrect to attribute the decline in morbidity to the (often simultaneous) introduction of chemotherapy and BCG vaccination. While the introduction of BCG vaccination of the newborn might have a pronounced effect on the incidence of infant tuberculosis, the impact of effective case-finding and treatment would also be most noticeable in this age group. For this reason, reports that merely show a decline in infant tuberculosis after the introduction of BCG vaccination are not considered here.

An interesting analysis of morbidity statistics for different countries was made by Bjartveit & Waaler, who studied the association between the decline of tuberculosis in various age groups and the age at which vaccination was given.[f] This association was quite pronounced and thus provided evidence of the efficacy of BCG vaccination. In one of the countries included in the analysis, BCG was given to the newborn, and the conclusions as regards efficacy would appear to apply to BCG vaccination of this age group. Ehrengut compared the decline of the mortality from tuberculous meningitis and miliary tuberculosis in Hamburg, where BCG vaccination had been given to the newborn since 1953, with that in Bavaria where there has been no such vaccination programme.[g] In Hamburg the decline was much faster, and during the period 1961–70 there was only 1 death in comparison with the 65 deaths recorded in Bavaria.

In May 1975, BCG vaccination was suspended in the Federal Republic of Germany because a new vaccine had given rise to untoward reactions. Whereas in 1973 and 1974, the official statistics showed that the incidence of tuberculosis in the 0–1-year age group was 35

[f] BJARTVEIT, K. & WAALER, H. *Bulletin of the World Health Organization*, 33: 289 (1965).

[g] EHRENGUT, W. *Pädiatrische Fortbildungkurse für die Praxis*, 11: 529 (1972).

and 33, respectively, 79 cases were observed between 1 September 1975 and 1 September 1976.[h] In this case, the causal relationship seems to be beyond doubt, but as the data in 1975–76 were collected by questionnaire the comparability may be questioned.

In retrospective studies comparison with a control group from the same population is sometimes possible, the best available control group being generally those who refused vaccination. Although in these cases the vaccinated and unvaccinated groups are self-selected, their comparability may be quite good, especially if the groups do not represent extremely large or small proportions of the eligible population. The comparability may be verified from exposure to tuberculosis, incidence of other diseases and disorders, accidents, etc. Some doubts with regard to comparability may nevertheless remain, and the value of the observations, therefore, depends largely on the magnitude of any difference observed between the groups. Statistical significance tests should be used with caution, and the protective effect of the vaccination is generally difficult to estimate. Some examples of studies of this kind are given below.

Among the children who resided in the City of Manchester and were born in the period 1951–60, 25 478 were born in a certain group of hospitals. BCG vaccination was offered for all these newborns, and was accepted for 10 326. Subsequently, from clinical records, it was found that of the children in the area who had tuberculosis during this period, 40 had been born in the hospitals of this group. All 40 cases appeared to have occurred in the 15 152 unvaccinated children.[i] Self-selection cannot reasonably be invoked to explain this difference in incidence. During the observation period the vaccination coverage increased, whereas the risk of tuberculosis decreased. Simple comparison of those vaccinated with those not vaccinated would produce a spurious beneficial effect of the vaccination, but obviously not of the extent observed.

The results have recently been published[j] of a retrospective study that concerned 6364 infants who were vaccinated at birth, in Hamburg in 1954, and 9524 who were not. Up to 1971, 9 of the vaccinated and 130 of the unvaccinated children had developed tuberculosis. Of the 30 370 children born in 1963, 27 371 were vaccinated and 2 999 were not. There were 11 cases of tuberculosis among the vaccinated and 16 cases among the unvaccinated children over the 8-year follow-up period. It is interesting to note that the secular trend in tuberculosis morbidity between 1954 and 1963 in the vaccinated and the unvaccinated children was similar. This would have been expected if exposure to tuberculosis infection had been the same in the two groups.

In 1965–67 in China (Province of Taiwan), 109 cases of tuberculous meningitis were observed in the 0–5-year age group. Only 4 cases out of the 109 had a BCG scar, whereas 34% of all the children had been vaccinated.[k]

In Hong Kong, between July 1971 and September 1974, there were 159 cases of confirmed tuberculosis in children born after July 1966, among which were 42 cases of meningitis and 23 of miliary tuberculosis. Of these, 150 were in the vaccinated and only 9 in the unvaccinated children. Nevertheless, as the vaccination coverage was very high, the average annual incidence was 1.0 and 1.7 per 10 000 children respectively.[l] The comparability of the two groups is open to some doubt since the unvaccinated group was very small in comparison with the vaccinated group.

---

[h] GENZ, H. *Deutsches medizinische Wochenschrift*, **102**: 1271 (1977).

[i] GRIFFITH, M. I. In: *Transactions of the Sixth Commonwealth Conference of Chest and Heart Association, London, 1962*, London, 1962, p. 47.

[j] EHRENGUT, W. & STELLMER, H. *Immunität und Infektion*, **5**: 35 (1977).

[k] GRZYBOWSKI, S. In: *Immunization in tuberculosis*, Bethesda, 1971, p. 133 (DHEW Publication No. [NIH] 72-68).

[l] ALLAN, W. G. L. *Bulletin of the International Union against Tuberculosis*, **51**: 239 (1976).

DISCUSSION

Taken at face value, the evidence presented above suggests that BCG vaccination of the newborn confers considerable protection against tuberculosis in infants and young children. On the other hand it should be realized that the evidence is both scanty and superficial. Thus, the fact that no study clearly showed a disappointing result, as has happened for vaccination of adolescents, may well be due to the insufficient number of studies undertaken or reported. Moreover, the actual degree of protection afforded by the variety of BCG products used cannot be determined accurately, and most of these products are no longer available and cannot be reproduced.

The studies mentioned refer mainly to vaccination during the first few days after birth. The strategy introduced recently in expanded immunization programmes, however, is to give BCG vaccination a few months after birth and the implications of this different timing with regard to the incidence of suppurative lymphadenitis and the degree of post-vaccination tuberculin sensitivity are currently being studied.

As regards protection, it may be reassuring to note that BCG vaccination invariably appeared effective in those studies in which tuberculosis disease appeared to occur relatively soon after infection, a situation that applies *ipso facto* in infant tuberculosis. Epidemiological factors that could impair the effect of BCG vaccination in adolescents, such as sensitization with atypical mycobacteria and repeated infection, are less likely to play a role in young infants. Nevertheless it is highly desirable that both controlled prospective studies and, where possible, epidemiological evaluation should be initiated as soon as possible.